INTELLECTUAL PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKS / GEOGRAPHICALINDICATION

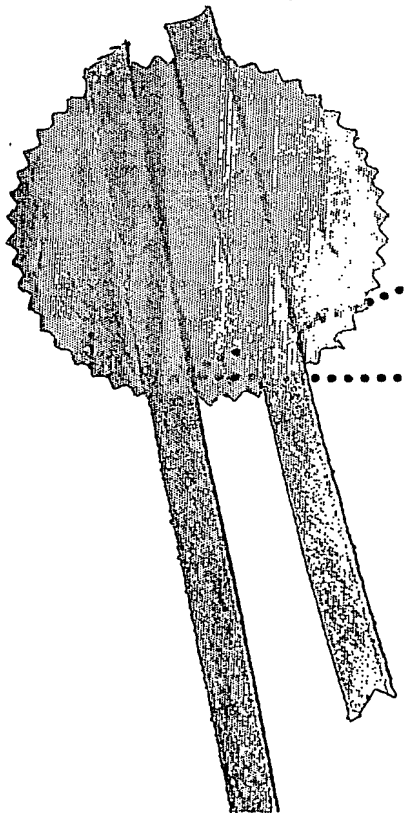
सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Complete Specification filed on 04/11/2003 in respect of Patent Application No.1158/MUM/2003 of M/S. CIPLA LIMITED, 289, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India, An Indian Company incorporated under the Companies Act,1956.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.



Dated this 17th day of December 2004.

(R.BHATTACHARYA)
ASSTT.CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See section 5(2), 7, 54 and 135; rule 39]

1. We,

   (a) M/S. CIPLA LIMITED

   (b) 289, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India

   (c) Indian company incorporated under the Companies Act 1956

2. Hereby declare –

   (a) that we are in possession of an invention titled **"NOVEL PROCESS FOR THE PREPARATION OF POLYMORPHS OF SELECTIVE SEROTONIN REUPTAKE INHIBITOR"**

   (b) that the Complete Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

(a) Kankan, Rajendra Narayanrao
(b) A-3/5, N.B.D. Society
N.S.S.Road, Ghatkopar
Mumbai 400 084
Maharashtra, India
(c) Indian National

(a) Rao, Dharmaraj Ramachandra
(b) 4/403, Garden Enclave,
Pokhran Road 2
Thane(W) 400 601
Maharashtra, India
(c) Indian National

1158/mum/2003

4/11/2003

Received Rs. 3000/- in Cash
Cheque/M.O./P.O. dt. 4/11/03
Vide Entry No. 5424 in the Register of Patents, Bombay
4-11-03

(a) **Narayan, Bhanu Manjunath**
(b) 103/Sarita Co-Op Hsg Society
I. C. Colony, Borivili (W)
Mumbai 400 103
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Kankan, Rajendra Narayanrao)

(Rao, Dharmaraj Ramachandra)

(Narayan, Bhanu Manjunath)

07. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:

(a) Complete specification (2 copies)

(b) Statement and Undertaking on Form 3

(c) Copy of Form 26 (Original Power of attorney in our favour has been submitted with Application No. 168/MUM/2003)

(d) Fee Rs.3000/- in cheque bearing No.525168 dated 4th Nov 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 4th day of Nov. 2003

DR. GOPAKUMAR G. NAIR
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road,
Kandivli(East) Mumbai – 400 101

To
The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

COMPLETE SPECIFICATION
[See section 10; rule 13]

"NOVEL PROCESS FOR THE PREPARATION OF POLYMORPHS OF SELECTIVE SEROTONIN REUPTAKE INHIBITOR"

(a) **CIPLA LTD.**

(b) **289, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India**

(c) Indian Company incorporated under the Companies Act 1956

The following specification particularly describes the nature of the invention and the manner in which it is to be performed:

Duplicate

1158/mum/2005
4/11/2005

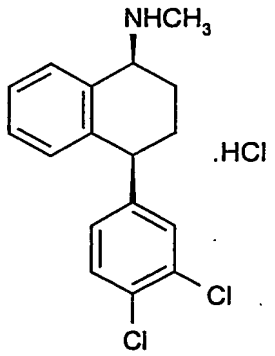
NOVEL PROCESS FOR THE PREPARATION OF POLYMORPHS OF SELECTIVE SEROTONIN REUPTAKE INHIBITOR

FIELD OF THE INVENTION

The present invention relates to a novel processes to manufacture various crystalline ploymorphic forms of sertraline hydrochloride from either sertraline base or sertraline acetate. The process is rugged and suitable for large scale manufacture of various forms of sertraline hydrochloride namely, form II, form III, form IV and form V.

BACKGROUND OF THE INVENTION

Sertraline hydrochloride,(1S-cis)-4-(3,4 dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride, having the formula 1 is approved, under the trademark Zoloft.RTM., by the U.S. Food and Drug Administration, for the treatment of depression, obsessive-compulsive disorder and panic disorder.



Formula 1

U.S. Patent No. 4,536,518 ("the '518 patent") describes the preparation of sertraline hydrochloride with a melting point of 243-245° C by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride. The solid state properties of the sertraline hydrochloride so produced are not otherwise disclosed.

U.S. Patent No. 5,734,083 describes the preparation of a form of sertraline hydrochloride denominated polymorph "T1."

According to U.S. Patent No. 5,248,699 ("the '699 patent"), the sertraline hydrochloride produced by the method of the '518 patent has a crystalline form denominated "Form II" The '699 patent discloses four other polymorphs of sertraline hydrochloride designated Forms I, III, IV, and V, and characterizes them by single crystal x-ray analysis, powder x-ray diffraction, infra-red spectroscopy, and differential scanning calorimetry. The '699 patent reports that Form II is produced by rapid crystallization of sertraline hydrochloride from an organic solvent, including isopropyl alcohol, ethyl acetate or hexane, and generally describes methods for making sertraline hydrochloride Forms I-V. According to this patent, the preferential formation of Forms I, II or IV in an acidic solution consisting of isopropyl alcohol, hexane, acetone, methyl isobutyl ketone, glacial acetic acid or, preferably, ethyl acetate, depends on the rapidity of crystallization. The only method described in this patent for making Forms II and IV is by the rapid crystallization of sertraline hydrochloride from an organic solvent such as those listed above.

US patent no 6,452,054 describes novel polymorphic Forms XI, XII, XIII, XIV, XV and XVI of sertraline hydrochloride, processes for preparing them, methods of using them to treat disease, methods of using them to make other sertraline hydrochloride forms, and to pharmaceutical dosages containing the novel forms.

US patent no 6,495,721 discloses novel methods to make Form II of sertraline hydrochloride. Sertraline hydrochloride Form II may be produced directly form sertraline base or sertraline mandelate. It may also be produced from sertraline hydrochloride.

United States Patent 6,500,987 is directed to forms II, III, V, VI, VII, VIII, IX and X of sertraline hydrochloride and novel methods for their preparation.

United States Patent 6,600,073 describes novel methods for the preparation of sertraline hydrochloride Forms III, V, VI, VII, VII, IX and X.

United States Patent Application 0020183555 relates to a process for making sertraline hydrochloride Form II comprising the steps of dissolving sertraline base or sertraline mandelate in an organic solvent to form a solution; adding hydrogen chloride to the solution; heating the solution to a temperature between about room temperature and about reflux for a time sufficient to induce the formation of sertraline hydrochloride Form II; and isolating sertraline hydrochloride Form II.

US patent application 20030023117 describes new and novel polymorphic Forms XI, XII, XIII, XIV, XV and XVI of sertraline hydrochloride, processes for preparing and methods of using them to treat disease, methods of using them to make other sertraline hydrochloride forms, and to pharmaceutical dosages containing the novel forms.

US patent application 20030055112 describes forms II, III, V, VI, VII, VIII, IX and X of sertraline hydrochloride and novel methods for their preparation. According to the present invention, sertraline hydrochloride polymorph II may be produced by slurrying sertraline hydrochloride polymorph VI in aprotic organic solvent. Sertraline hydrochloride polymorphic form III may be produced by heating sertraline hydrochloride polymorphs V and VI. Sertraline hydrochloride forms V and VI may be produced from either sertraline hydrochloride or sertraline base by crystallization. Sertraline hydrochloride Form VII may be produced by suspending sertraline chloride polymorph V in water, followed by filtration. Sertraline hydrochloride Forms VIII and IX may be produced by suspending sertraline base in water followed by acidification and filtration. Sertraline hydrochloride Form X may be produced by suspending sertraline hydrochloride in benzyl alcohol with heating, followed by filtration.

US patent no 6,517,866 deals with various salts of sertraline such as sertraline aspartate, sertraline acetate, sertraline lactate and sustained release dosage forms thereof.

SUMMARY OF THE INVENTION

The present invention relates to a process for making sertraline hydrochloride polymorphs Form II, Form III, Form IV and Form V.

The present invention further relates to a novel and cost effective process for making sertraline hydrochloride Form II form III, form IV and form V, comprising the steps of treating sertraline acetate in suitable solvents with hydrogen chloride gas to give either form II, form III or form IV depending on the solvent and temperature.

The present invention still further relates to a process for making a sertraline hydrochloride Form V comprising the steps of dissolving sertraline base in acetic acid and treating with hydrochloric acid. and isolating sertraline hydrochloride Form V.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides new processes for making sertraline hydrochloride from sertraline acetate. Sertraline acetate is prepared as per the process described in US patent No. 6,517,866 from sertraline base.

Sertraline base is dissolved in a suitable solvent. Suitable solvents include ethyl acetate, toluene, acetone, t-methyl-butyl ether, hexane and cyclohexane, and mixtures thereof. The pH of the sertraline base solution is lowered by the addition of glacial acetic acid to precipitate sertraline acetate. The most preferred solvents are n-hexane and toluene.

In a preferred embodiment of the present invention, sertraline acetate is suspended / dissolved in suitable solvents and hydrogen chloride is added to convert the sertraline acetate into sertraline hydrochloride.

Hydrogen chloride used may be added as a gas or a solution with an organic solvent, such as a solution of isopropyl alcohol and hydrogen chloride, n-butanol and hydrogen chloride, acetone and hydrogen chloride, or the like.

In another preferred embodiment of this invention to make form II of sertraline hydrochloride, sertraline acetate is suspended/ dissolved in suitable solvents such as isopropanol, toluene,

methanol, ethanol, ethyl acetate or mixtures thereof at ambient to elevated temperatures ranging from 30°C to 80°C, hydrogen chloride is added to adjust the pH of the reaction mixture to between 1 to 2. The addition of hydrogen chloride to sertraline acetate in suitable solvents is exothermic and the temperature rises from ambient to 60°C - 65°C. The mixture is then cooled gradually to ambient with no external cooling provided over a few hours. The product so obtained is isolated and dried at about 80°C under vacuum to give sertraline hydrochloride form II.

The most preferred solvent for making sertraline hydrochloride form II is a mixture of isopropanol and toluene. The solvents are preferably taken in ratios ranging from 1% to 95% toluene. The more preferred ratio being in the range of 2 – 8% toluene. The most preferred ratio being 3% - 5% of toluene in isopropanol.

In another preferred embodiment of this invention to make sertaline hydrochloride form III. sertraline acetate is suspended/ dissolved in suitable solvents such as isopropanol, toluene. methanol, ethanol, ethyl acetate or mixtures thereof at ambient to elevated temperatures ranging from 30°C to 80°C, hydrogen chloride is added to adjust the pH of the reaction mixture to between 1 to 2. The addition of hydrogen chloride to sertraline acetate in suitable solvents is exothermic and the temperature rises from ambient to 60°C - 65°C. The mixture is then cooled rapidly with aid of an ice bath and the temperature is brought down to 15°C to 18°C with in 15 minutes. The product so obtained is isolated by filtration and dried at about 80°C under vacuum to give sertraline hydrochloride form III.

The most preferred solvent for making sertraline hydrochloride form II is a mixture of isopropanol and toluene. The solvents are preferably taken in ratios ranging from 1% to 95% toluene. The more preferred ratio being in the range of 2 – 8% toluene. The most preferred ratio being 3% - 5% of toluene in isopropanol.

In another preferred embodiment of this invention to make sertaline hydrochloride form IV, sertraline acetate is suspended/ dissolved in suitable solvents such as isopropanol, toluene, methanol, ethanol, ethyl acetate or mixtures thereof at ambient to elevated temperatures ranging from 30°C to 80°C, hydrogen chloride is added to adjust the pH of the reaction mixture to between

to 2. The addition of hydrogen chloride to sertraline acetate in suitable solvents is exothermic and he temperature rises from ambient to 60°C - 65°C. The mixture is then cooled rapidly with aid of in ice bath and the temperature is brought down to 15°C to 18°C within 30 minutes. The product so obtained is isolated and dried at 60°C in a fluid bed drier to give sertraline hydrochloride form IV.

The most preferred solvent for making sertraline hydrochloride form IV is isopropanol.

In another preferred embodiment of this invention to make sertaline hydrochloride form V, sertraline acetate is suspended/ dissolved in water and hydrochloric acid is added to adjust the pH of the reaction mixture to between 1 to 2. The mixture is stirred at about 25°C for 2 hours. The product so obtained is isolated and dried at 60°C under vacuum to give sertraline hydrochloride form V.

In another preferred embodiment of this invention to make sertaline hydrochloride form V, sertraline base is dissolved in acetic acid. Water is added as a diluent and aqueous hydrogen chloride is added to adjust the pH of the reaction mixture to between 1 to 2. after precipitation of the product, the reaction is further diluted with water before isolation of the product. The product so obtained is isolated and dried at 65°C in a fluid bed drier to give sertraline hydrochloride form V.

The following examples describe the process of the invention and are in no way limiting the scope of the invention.

Reference Examples

Preparation of sertraline acetate

30 gms of sertraline base is dissolved in 200 ml of toluene under stirring at room temp.
5 ml acetic acid to the clear toluene solution and stirred for 1 hr. at 25°C to obtain a thick white precipitate. The solids are filtered and re-slurried in 100 ml toluene for 30 minutes and filtered. The product is dried under vacuum at 60°C for 5 – 6 hours to give sertraline acetate.

Preparation of sertraline acetate

71 gms of sertraline base is dissolved in 350 ml of n-Hexane under stirring at room temperature. 14 ml acetic acid is added to the clear solution and stirred for 10 minutes at 25°C and refluxed at 60°C for 30 minutes to obtain a thick white precipitate. The precipitated solid is filtered. The product is dried in a fluid bed dryer at 60°C for 3 – 4 hours to give sertraline acetate.

Example 1

Preparation of sertraline hydrochloride form II

20 grams of sertraline acetate is suspended in a mixture of 100 ml of isopropyl alcohol and 4 ml toluene. The mixture is heated to 50°C to get a clear solution and dry hydrogen chloride gas is bubbled to adjust the pH between1 to 2. The reaction is exothermic and the temperature rises to 60°C. The reaction mixture was cooled gradually to room temperature. The precipitated solids is filtered and washed with isopropyl alcohol and dried under vacuum at 80°C for 4 – 5 hours to give sertraline hydrochloride form II.

Example 2

Preparation of sertraline hydrochloride form III

20 grams of sertraline acetate is suspended in a mixture of 100 ml of isopropyl alcohol and 4 ml toluene. The mixture is heated to 50°C to get a clear solution and dry hydrogen chloride gas is bubbled to adjust the pH between 1to 2. The reaction is exothermic and the temperature rises to 60°C. The reaction mixture was cooled rapidly to 15°C to 20°C within 15 – 20 minutes with an ice bath. The precipitated solid is filtered and washed with isopropyl alcohol and dried under vacuum at 80°C for 4 – 5 hours to give sertraline hydrochloride form III.

Example 3

Preparation of sertraline hydrochloride form IV

50 grams of sertraline acetate is suspended in 250 ml of isopropyl alcohol at room temperature. The mixture is heated to 50°C to get a clear solution and dry hydrogen chloride gas is bubbled to reduce the pH between 1-2.The reaction mixture is cooled 15-20°Cwithin 30 minutes under stirring. The precipitated solids is filtered and washed with isopropyl alcohol and dried in a fluid bed drier at 60°C for 4-5 hour as to give sertraline hydrochloride form IV

Example 4

Preparation of sertraline hydrochloride form V

10 gms of sertraline acetate is dissolved in 100 ml of water at room temperature under stirring. The solution is filtered to obtain a clear solution. To the clear filtrate 5 ml concentrated hydrochloric acid is added drop wise under stirring to adjust pH between 1 to 2. The precipitated solids are stirred for 1 hour at 25°C and filtered. The solids are dried under vacuum at 60°C for 8 hours to give sertraline hydrochloride form V.

Example 5

Preparation of sertraline hydrochloride form V from sertraline base

300 gms of sertraline base is dissolved in 600 ml acetic acid at room temperature and stirred to obtain a clear solution. To the above clear solution, 3000 ml water is added under stirring in 20 min at 25°C. The reaction mixture is cooled to 5° - 10° C and stirred for 1 hr. Concentrated hydrochloric acid is added to the above clear solution and the pH adjust to between 1 to 2 at 5- 10 °C. The reaction mixture is stirred for 15 minutes and the sertraline hydrochloride precipitates during this period. 600 ml of water is charged and the reaction mixture stirred at 10-15°C. for 1 hour. The solids are filtered and dried in a Fluid Bed Dryer at 60-70°C for 4-5 hrs. to give form V of sertraline hydrochloride

We Claim,

1. A process for the preparation of sertraline hydrochloride by
    a. Suspending/dissolving sertraline base or acetate in suitable solvents
    b. Adjusting the pH of the mixture with hydrogen chloride either in anhydrous form or aqueous form at elevated temperatures ranging between 25°C to 65°C
    c. Cooling the reaction mixture
    d. Isolating and drying to get sertraline hydrochloride.
2. A process according to claim 1 to make sertaline hydrochloride form II by
    a. Suspending/dissolving sertraline acetate in suitable solvents
    b. Adjusting the pH of the mixture with hydrogen chloride gas at elevated temperatures ranging between 40°C to 65°C
    c. Cooling the reaction mixture
    d. Isolating and drying the sertraline hydrochloride to get from II.
3. A process according to claim 2 wherein the sertraline acetate is suspended/dissolved in solvents such as methanol, ethanol, isopropanol, ethyl acetate, toluene or mixtures thereof.
4. A process according to claim 2 wherein the solvent used is a mixture of isopropanol and toluene.
5. A process according to claim 4 wherein toluene is present between 2 to 8%.
6. A process according to claim 2 wherein the pH of the mixture is adjusted to between 1 – 2.
7. A process according to claim 6 wherein the pH is adjusted at temperatures between 45°C to 65°C.
8. A process according to claim 2 wherein the cooling is done gradually over a couple of hours to bring the temperature from 60°C to 25°C - 20°C.
9. A process according to claim 8 wherein the cooling is done over than 2 hours.
10. A process according to claim 1 to make sertaline hydrochloride form III by
    a. Suspending/dissolving sertraline acetate in suitable solvents
    b. Adjusting the pH of the mixture with hydrogen chloride gas at elevated temperatures ranging between 40°C to 65°C
    c. Cooling the reaction mixture
    d. Isolating and drying the sertraline hydrochloride to get from III.

11. A process according to claim 10 wherein the sertraline acetate is suspended/dissolved in solvents such as methanol, ethanol, isopropanol, ethyl acetate, toluene or mixtures thereof.
12. A process according to claim 10 wherein the solvent used is a mixture of isopropanol and toluene.
13. A process according to claim 12 wherein toluene is present between 2 to 8%.
14. A process according to claim 10 wherein the pH of the mixture is adjusted to between 1 – 2.
15. A process according to claim 14 wherein the pH is adjusted at temperatures between 45°C to 65°C.
16. A process according to claim 10 wherein the cooling is done rapidly over a few minutes to bring the temperature from 60°C to 25°C – 20°C.
17. A process according to claim 16 wherein the cooling is done in less than 1 hour.
18. A process according to claim 1 to make sertaline hydrochloride form IV by
    a. Suspending/dissolving sertraline acetate in suitable solvents
    b. Adjusting the pH of the mixture with hydrogen chloride gas at elevated temperatures ranging between 40°C to 65°C
    c. Cooling the reaction mixture
    d. Isolating and drying the sertraline hydrochloride to get from IV.
19. A process according to claim 18 wherein the sertraline acetate is suspended/dissolved in solvents such as methanol, ethanol, isopropanol, ethyl acetate, toluene or mixtures thereof.
20. A process according to claim 18 wherein the solvent used is isopropanol.
21. A process according to claim 18 wherein the pH of the mixture is adjusted to between 1 – 2.
22. A process according to claim 21 wherein the pH is adjusted at temperatures between 45°C to 65°C.
23. A process according to claim 18 wherein the cooling is done rapidly bring the temperature from 60°C to 25°C - 20°C.
24. A process according to claim 23 wherein the cooling is done in less than one hour.over 30 minutes

25. A process according to claim 1 to make sertaline hydrochloride form V by
    a. Suspending/dissolving sertraline acetate in suitable solvents
    b. Adjusting the pH of the mixture with aqueous hydrochloric acid at ambient temperatures ranging between 30°C to 25°C
    c. Isolating and drying the sertraline hydrochloride to get from V.
26. A process according to claim 25 wherein the sertraline acetate is suspended/dissolved in solvents such as methanol, ethanol, isopropanol, ethyl acetate or water or mixtures thereof.
27. A process according to claim 25 wherein the solvent used is water.
28. A process according to claim 25 wherein the pH of the mixture is adjusted to between 1 – 2.
29. A process according to claim 28wherein the pH is adjusted at temperatures between 35°C to 25°C.
30. A process according to claim 1 to make sertaline hydrochloride form V by
    a. Suspending/dissolving sertraline base in suitable solvents
    b. Adjusting the pH of the mixture with aqueous hydrogen chloride
    c. Cooling the reaction mixture
    d. Isolating and drying the sertraline hydrochloride to get from V.
31. A process according to claim 30 wherein the sertraline base is suspended/dissolved in acetic acid.
32. A process according to claim 30 wherein the solvent used is acetic acid.
33. A process according to claim 30 wherein the pH of the mixture is adjusted to between 1 – 2.
34. A process according to claim 30 wherein the cooling is done gradually to bring the temperature from 30°C to 5°C - 0°C.

Dated this the 4th day of Nov. 2003

Dr. GOPAKUMAR G. NAIR
Agent for the Applicant

ABSTACT

The present invention is directed to Form II, III IV and V of sertraline hydrochloride and novel methods for its preparation. According to the present invention, the various polymorphs of sertraline hydrochloride may be produced, either, directly from sertraline base or sertraline acetate.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB04/004672

International filing date: 04 November 2004 (04.11.2004)

Document type: Certified copy of priority document

Document details: Country/Office: IN
Number: 1158/MUM/2003
Filing date: 04 November 2003 (04.11.2003)

Date of receipt at the International Bureau: 09 February 2005 (09.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☑ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☑ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.